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Panitumumab and Cetuximab Toxicity Management

Accompanies: Clinical Practice Guideline GI-003

Cancer Care Alberta

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The assessment, prevention, rehabilitation and management strategies outlined in this summary and accompanying guideline apply to adult cancer patients with advanced colorectal cancer. Refer to the full clinical practice guideline for a detailed description of the clinical questions, recommendations, guideline development methodology, and references.

Background

This resource has been created to ensure the safe administration of panitumumab or cetuximab (anti-EGFR therapy) to patients with advanced colorectal cancer in Alberta.

For more information on recommended regimens please see the Metastatic Colorectal Cancer clinical practice guideline.

Adverse Events

Standard monitoring for adverse effects should occur through each cycle. The following adverse effects warrant specific attention:

Cutaneous Toxicities (e.g., erythema, rash, follicular eruption, desquamation, xerosis, pruritus):

Toxicity	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Erythema, Rash, Follicular Eruption, Desquamation, and/or Ulceration	Painless erythema Macular or papular follicular eruption *without* associated symptoms	Painful erythema Macular or papular follicular eruption *with* associated symptoms (e.g.: pruritus, pain) Localized desquamation (<50% body surface area) Superficial ulceration < 2 cm	Generalized erythroderma Severe macular or papular follicular eruption Generalized desquamation (≥50% body surface area) — sloughing not just dry flaking Ulceration ≥ 2 cm	Life threatening or disabling Generalized exfoliation or ulceration
	Provide symptomatic care Continue anti-EGFR therapy	Provide symptomatic and local skin care Continue anti-EGFR therapy	Provide symptomatic care, debridement, primary closure, etc. Withhold anti-EGFR therapy and reassess in two weeks If cutaneous toxicities regress to grade ≤2, then resume with 20% dose reduction	Provide supportive care, skin grafting, tissue reconstruction, etc. Permanently discontinue anti-EGFR therapy

Toxicity	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Xerosis (Dry Skin) and Pruritus	Asymptomatic xerosis Mild or localized pruritus	Symptomatic xerosis, but not interfering with activities of daily living Intense or widespread pruritus	Xerosis or pruritus that interferes with activities of daily living	Not applicable
	Apply moisturizing creams	Apply moisturizing creams Suggest oral anti-histamine	Apply moisturizing creams Suggest oral anti-histamine Withhold panitumumab and reassess in two weeks	Not applicable

Other cutaneous toxicities include hair alteration (e.g.: thinning, trichomegaly), telangiectasiae, and nasal mucositis.

The STEPP trial suggests that, when compared to reactive skin treatment, "pre-emptive" skin treatment (started twenty-four hours before the first dose of panitumumab) reduces the incidence of grade 2, 3, and 4 skin toxicities from 62% to 29%, delays the development of severe skin toxicities, and improves the patient's quality of life during the period of prophylactic use.[1]

Skin Toxicity Evaluation Protocol with Panitumumab Recommendations[1]

- Apply a skin moisturizer (e.g., Lubriderm, Vaseline Intensive Care, Glaxal Base) to the face, hands, feet, neck, back, and chest daily in the morning upon rising.
- Apply a topical steroid (e.g., 1% hydrocortisone cream) to face, hands, feet, neck, back, and chest at bedtime.
- Take doxycycline 100 mg po BID for its anti-inflammatory effects.
- Apply a PABA-free sunscreen with at least SPF 15 and UVA/UVB protection to sun-exposed areas before going outside.

Patients should be encouraged to:

- Apply moisturizing creams frequently to prevent skin dryness, fissures, or pulpitis sicca
- Use sunscreens and limit sun exposure
- Avoid the excessive use of soaps and bathing
- Avoid medications for acne vulgaris (benzoyl peroxide, antibiotic gels, and retinoids can irritate the skin, result in excessive dryness, and aggravate the rash and pruritus).

Further information about rash management can be found in the clinical practice guideline for Prevention and Treatment of Acneiform Rash in Patients Treated with EGFR Inhibitor Therapies.

Painful inflammation around the nails (paronychia) may lead to painful fissures and pyogenic granulomas. Patients should be encouraged to avoid wearing tight- or ill-fitting shoes. Relief can often

be achieved by the use of Epsom salt soaks. Secondary infections warrant the use of a topical (or, if severe, systemic) antibiotic or antifungal agents (e.g., mupirocin ointment).

Ocular irritation (e.g., dry eyes, conjunctivitis, crusting, hyperemia, lacrimation) may require moisturizing eye drops, warm soaks, and/or ophthalmic antibiotics.

Diarrhea:

Toxicity	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Diarrhea	Increase of one to three stools per day *or* mild increase in ostomy output over baseline	Increase of four to six stools per day *or* moderate increase in ostomy output over base-line that fails to interfere with activities of daily living	Increase of seven or more stools per day *or* severe increase in ostomy output over baseline *or* interferes with activities of daily living	Life threatening consequences (e.g.: hemodynamic collapse)
	Consider Loperamide Provide symptomatic care Continue anti-EGFR therapy	Consider Loperamide Provide symptomatic care and intravenous hydration Continue anti-EGFR therapy	Consider Loperamide Provide intravenous hydration and hospitalization for supportive care Withhold anti-EGFR therapy and reassess in two weeks If diarrhea regresses to grade ≤1, then resume with 20% dose reduction	Provide intensive care Permanently discontinue anti-EGFR therapy

Hypomagnesemia: Monitor electrolyte, magnesium, and calcium levels during and for eight weeks *beyond* completion of therapy. See appendix for further details.

Toxicity	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Hypomagnesemia	Magnesium: 0.50 to 0.70 mM	Magnesium: 0.40 to 0.49 mM	Magnesium: 0.30 to 0.39 mM	Magnesium: <0.30 mM
	If asymptomatic, continue anti-EGFR therapy	If asymptomatic, continue anti-EGFR therapy	If symptomatic, withhold anti-EGFR therapy and reassess in two weeks	Withhold anti-EGFR therapy and reassess in two weeks
	Consider pre-emptive oral supplementation See appendix	Consider pre-emptive oral supplementation See appendix	Provide oral supplementation See appendix	Provide oral supplementation See appendix
	Contraindications to magnesium replacement: · Pre-existing diarrhea · Acute abdominal pain, nausea, or emesis · Heart block · Renal impairment · Myasthenia gravis or other neuromuscular disease		If hypokalemia and/or QT interval prolongation co-exist, consider magnesium sulfate 4,000 mg over at least two hours	If hypokalemia and/or QT interval prolongation co-exist, consider magnesium sulfate 4,000 mg over at least two hours

		If toxicity regresses to grade ≤2, resume anti-EGFR therapy	If toxicity regresses to grade ≤2, resume anti-EGFR therapy

Fatigue, Asthenia, Lethargy, or Malaise:

Toxicity	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Fatigue, Asthenia, Lethargy, or Malaise	Mild fatigue over baseline	Causes difficulty performing some activities of daily living	Interferes with activities of daily living	Disabling
	Exclude laboratory and other confounding abnormalities Provide symptomatic care Continue anti-EGFR therapy	Exclude laboratory and other confounding abnormalities Provide symptomatic care Continue anti-EGFR therapy	Exclude laboratory and other confounding abnormalities Provide symptomatic care Withhold anti-EGFR therapy and reassess in two weeks If fatigue regresses to grade ≤1, then resume with 20% dose reduction	Exclude laboratory and other confounding abnormalities Provide symptomatic care Permanently discontinue anti-EGFR therapy

Hypersensitivity Reactions: Infusion reactions have been reported at a rate of about 1%. Remain vigilant for fever, chills, rash, urticaria, bronchospasm, hypotension, and anaphylactic reactions. For more information, refer to the Acute Infusion Related Adverse Events to Chemotherapy and Monoclonal Antibodies clinical practice guideline.

Interstitial Lung Disease: Represents a rare (0.5%), rapidly progressive, and potentially fatal complication. Assess respiratory symptoms, especially during the first few months of therapy. Initial signs include dyspnea with or without a cough or low-grade fever.

Toxicity	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening)
Interstitial Lung Disease	Asymptomatic (no dyspnea or cough) Patchy radiologic changes that involve less than 25% of lung volume	Dyspnea, low-grade fever, or cough that fails to interfere with activities of daily living Patchy radiologic changes that involve 25 to 49% of lung volume	Dyspnea, low-grade fever, or cough that interferes with activities of daily living Widespread infiltrates that involve 50 to 74% of lung volume	Life threatening Widespread infiltrates that involve ≥75% of lung volume
	Exclude confounding etiology Permanently discontinue anti-EGFR therapy	Provide symptomatic care (e.g.: oxygen if S_aO_2 ≤89%) Exclude confounding etiology Permanently discontinue anti-EGFR therapy	Provide symptomatic care (e.g.: oxygen if S_aO_2 ≤89%) Exclude confounding etiology Permanently discontinue anti-EGFR therapy	Provide intensive care for ventilatory support Permanently discontinue anti-EGFR therapy

Constitutional Toxicities and Pain: Provide the usual supportive management for anorexia, nausea, emesis, pain, constipation, and fever (neutropenia is not expected with anti-EGFR therapy).

References

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Appendix: Hypomagnesemia

Magnesium is an important electrolyte that functions as a cofactor for enzymatic reactions involved in glucose utilization, muscle contraction and nerve conduction, and the synthesis of fat, proteins, nucleic acids, and coenzymes.[2] Hypomagnesemia contributes to a broad range of clinical problems; they range from anorexia, nausea, emesis, weakness, paraesthesias, and muscle cramps to ataxia, seizures, neuropsychiatric disturbances (e.g.: depression, delirium, psychosis), dysrhythmias, and respiratory failure.[2]

Hypomagnesemia results from protracted emesis or diarrhea, the chronic use of diuretics and proton pump inhibitors, diabetes mellitus type 2 and alcoholism, malabsorption or resection/bypass of the small intestine (especially the ileum), renal injury (e.g.: aminoglycosides, Cisplatin, Carboplatin, etc.), and defective renal tubular magnesium reabsorption. Anti-EGFR therapies induce hypomagnesemia by this latter mechanism[3] with an overall relative risk for all-grade hypomagnesemia of 5.83 and an overall relative risk for severe hypomagnesemia of 10.51.[4] Although the evidence is inconsistent in the literature, Vickers and colleagues[5] suggests that hypomagnesemia correlates with an inferior median overall survival. Given all of these factors, it is important to optimally manage this common problem.

Ingestion of magnesium salts predisposes to diarrhea, nausea, and abdominal cramps; however, catharsis generally occurs with elemental doses over 1,000 mg per day. In addition, oral magnesium interferes with the absorption of oral bisphosphonates (e.g.: Alendronate), antibiotics (e.g.: tetracyclines, quinolones), azole antifungals, levothyroxine, and other drugs.[6] Please refer to specialized references for drug interaction information.

A rapid increase in the serum levels is rarely required in the absence of life-threatening ventricular dysrhythmias. Further, doses of intravenous magnesium to correct low serum magnesium concentrations in the acute setting remain unlikely to correct chronic hypomagnesemia. Therefore, when rapid change is not required, oral magnesium provides a suitable option, especially for chronic replacement.[7]

Recommendations:

As there is limited evidence available regarding magnesium supplementation and anti-EGFR therapy the recommendations included are based on consideration of the available evidence and consensus of the GI Provincial Tumour Team.

1. Ensure optimal management of emesis, diarrhea, and diabetes
2. Address alcoholism
3. Curtail the use of loop and thiazide diuretics, where possible
4. Curtail the use of proton pump inhibitors, where possible
5. Avoid nephrotoxic agents (e.g.: aminoglycosides, cisplatin, etc.)
6. Encourage a diet high in magnesium (see Sources of Magnesium table)
7. Provide magnesium supplementation

Product/dosing examples*:

- Magnesium oxide 420-840 mg once daily to three times daily
- Magnesium glucoheptonate (Magnesium Rougier®) 15-75 mL four times daily
- Magnesium gluconate (Maglucate®) 500-1000 mg three times daily
- Magnesium complex 250 mg twice daily
- Magnesium hydroxide (Milk of Magnesia®)** 5-15 mL once daily to 4 times daily

* This is not an all-inclusive list of products or dosing recommendations. Starting with lower doses and daily divided doses may improve tolerance and reduce diarrhea. Monitor for magnesium levels and toxicity.

** Consider antacid activity of magnesium hydroxide may alter gastric and urinary pH and affect bioavailability or renal elimination of concurrent medications.

Sources of Magnesium[8]

Food	Per serving	Daily Value	Food	Per serving	Daily Value
Pumpkin seeds, roasted (1 oz)	156 mg	37%	Oatmeal, instant (1 packet)	36 mg	9%
Chia seeds (1 oz)	111 mg	26%	Kidney beans, canned (1/2 cup)	35 mg	8%
Almonds, dry roasted (1 oz)	80 mg	19%	Banana (1 medium)	32 mg	8%
Spinach, boiled (1/2 cup)	78 mg	19%	Salmon, Atlantic farmed and cooked (3 oz)	26 mg	6%
Cashews, dry roasted (1 oz)	74 mg	18%	Milk (1 cup)	24-27 mg	6%
Peanuts, oil roasted (1/4 cup)	63 mg	15%	Halibut, cooked (3 oz)	24 mg	6%
Cereal, shredded wheat (2 large biscuits)	61 mg	15%	Raisins (1/2 cup)	23 mg	6%
Soymilk, plain or vanilla (1 cup)	61 mg	15%	Bread, whole wheat (1 slice)	23 mg	5%
Black beans, cooked (1/2 cup)	60 mg	14%	Avocado, cubed (1/2 cup)	22 mg	5%
Edamame, shelled & cooked (1/2 cup)	50 mg	12%	Chicken breast, roasted (3 oz)	22 mg	5%
Peanut butter, smooth (2 tbsp)	49 mg	12%	Beef, ground 90% lean pan broiled (3 oz)	20 mg	5%
Potato, baked with skin (3.5 oz)	43 mg	10%	Broccoli, cooked (1/2 cup)	12 mg	3%
Rice, brown, cooked (1/2 cup)	42 mg	10%	Rice, white, cooked (1/2 cup)	10 mg	2%
Yogurt, plain low fat (8 oz)	42 mg	10%	Apple (1 medium)	9 mg	2%
Breakfast cereals, fortified with 10% of the DV for magnesium, 1 serving	42 mg	10%	Carrot, raw (1 medium)	7 mg	2%

National Institutes of Health (*https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/*) Based upon Recommended Dietary Allowances